REMARKS

Upon entry of the present amendment, claims 32, 33, 38, 42, 43, and 60-63 will be pending. Applicants have amended claims 32 and 33, added new claims 61-63, and canceled claims 1-31, 34-37, 39-41, 44-59 without prejudice. Support for the amendments and the new claim can be found throughout the specification, e.g., in Example 6.

Interview Summary

Applicants thank Examiner Long for the telephone interview on June 28, 2010, with applicants' representatives, Peter Fasse and Jeannie Wu, to discuss the rejections set forth in this office action. Examiner Long suggested potential claim amendments and evidence of non-obviousness, and also agreed to discuss this case with Examiner Woitach. Examiner Long called Peter Fasse on June 28, 2010, to convey Examiner Woitach's suggestion to narrow the claims to recite specific combinations of elements that achieved a protective response.

Withdrawn Rejection

Applicants note with appreciation that the Office has withdrawn the previous rejection under 35 U.S.C. § 103.

35 U.S.C. § 103

The Office rejected claims 1-3, 7, 11-14, 20-22, 32-35, 38, 42-43, and 57-60 as allegedly obvious over Felgner et al. (W090111092; "Felgner") in view of Huylebroeck et al. (Gene. June 1988, 66(2):163-81; "Huylebroeck") and further in view of Townsend et al . (Cell. November 1984, 39(1):13-25; "Townsend"). All of these references were cited in earlier office actions, and applicants maintain that the rejected claims are not obvious for at least the reasons set forth in applicants' replies to these earlier office action. However, for the sole purpose of moving this application towards allowance, applicants have canceled claims 1-31, 34-37, 39-41, 44-59 without prejudice, and amended claims 32 and 33. This rejection is traversed with respect to the presently amended claims.

The claims, as currently amended, are directed to a method comprising administering parenterally to the vertebrate, prior to infection by an H1N1 influenza virus, a plurality of the same plasmid vectors comprising DNA encoding an H1N1 influenza virus antigen operatively linked to a CMV promoter, wherein the plasmid vectors are administered with a gene gun, thereby eliciting a protective immune response comprising both a humoral and a cell-mediated immune response against the antigen, whereby the vertebrate is protected from disease caused by a subsequent infection by the H1N1 influenza virus.

Before applicants discuss the cited references, applicants would like to bring the Office's attention to the data disclosed in the present specification regarding gen guns. Example 6 of the specification describes administering to mice, using a gene gun, plasmids encoding an H1N1 influenza virus hemagglutinin linked to a CMV promoter. As the specification states (at page 29, line 20, to page 30, line 23):

> Gene gun-based acceleration of DNA-coated gold beads into the epidermis proved to be by far the most efficient method of DNA immunization, as shown in Table 8 ... These tests of gun-delivered DNA in the murine model demonstrated that as little as 0.4 μg of DNA was sufficient to achieve 95% survival. These survivors developed very limited to no signs of postchallenge influenza ... Thus, highly efficient immunizations were achieved by gene-gun delivery of DNA to the epidermis of mice. This method of immunization required 250-2500 times less DNA than the saline inoculations (0.4-0.00.4 μg as opposed to 100-200 μg of DNA) (See Tables 6 and 7).

Thus, applicants found that administration of DNA vaccines using a gene gun is surprising more effective than administering the DNA vaccine in saline, requiring much less DNA to protect a vertebrate from a subsequent infection by an influenza virus. The data in Example 9 further show that administration of DNA via gene guns also worked better than administration of alginate-encapsulated DNA in water via the mucosal route. See Table 13. Those of ordinary skill in the art would not have expected gene gun to be so much more effective than other routes of administration, since as stated in the specification (at page 29, lines 15-17), "[expression of the gene] is transient, with most of the expression being lost within 2-3 days due to normal sloughing of the epidermis." Moreover, data disclosed in the specification suggest that greater efficiency of

transfection of plasmids does not necessarily lead to better immunization. See page 26, lines 8-15. Therefore, it would not have been obvious that delivering DNA, e.g., into the epidermis, using gene guns would have achieved better immunization than other routes of administration.

Felgner fails to disclose or suggest the presently amended claims. Applicants maintain that while Felgner generally discloses the introduction of DNA or RNA into vertebrates for a variety of applications, including so-called immunization, applicants have found no actual data in Felgner to suggest that DNA vaccines can be used to successfully immunize a subject against subsequent infection from an H1N1 influenza virus, or any virus for that matter. Thus, applicants submit that skilled practitioners would not have expected a prophylactic DNA vaccine, administered to mice by gene guns with a DNA dosage of a low as 0.04 μg, to be successful based on the disclosure of Felgner. The Office pointed out that Felgner discloses administration of polynucleotides using a "vaccine gun." See the Office Action at page 8, line 4. It is not clear to the applicants whether the Office is suggesting that a vaccine gun reads on a gene gun, but applicants submit that a gene gun and a vaccine gun are different devices. A gene gun is a specialized device that delivers DNA-coated particles, e.g., gold beads, to animals, cells or plants. Those of ordinary skill in the art would know that a vaccine gun refers to a needle-less device that delivers liquid medication. See Exhibit A.[1] In any event, there is nothing in Felgner to suggest that administration of DNA vaccines using a gene gun would be a particularly efficient method to achieve a protective response against a subsequent infection by an influenza virus.

Huylebroeck does not remedy the deficiencies of Felgner. This reference discloses plasmid vectors for transient expression of DNA in animal cells (see, e.g., Abstract), and the use of these vectors to express H3N2 influenza hemagglutinin HA and H1N1 influenza matrix protein M_1 in cultured cells to study these viral proteins (see, e.g., at page 173, right column). As applicants set forth in the reply to the previous office action, there is nothing here that would have lead skilled practitioners to use these vectors to immunize vertebrates against later

[1] Downloaded from en.wikipedia.org/wiki/Jet_injector on July 6, 2010.

influenza infections. There is certainly nothing in this reference that would have led a skilled practitioner to use a gene gun to deliver plasmids to immunize vertebrates.

The Office also cited Townsend, but this reference similarly fails to rectify the deficiencies of Felgner and Huylebroeck. Townsend (at page 13, right column, the first full paragraph) used established cell lines expressing individual influenza genes "... to compare the roles played by the nucleoprotein and hemagglutinin molecules in target cell recognition by influenza A specific cytotoxic T cells." Like Huylebroeck, using transfected cells to study viral proteins *in vitro* does not provide any suggestion for a DNA vaccine that provides a protective immune response. Moreover, Townsend does not even suggest using gene guns to administer plasmids to vertebrates.

In summary, Felgner, Huylebroeck and Townsend, individually or in combination, fail to suggest the methods recited in the present claims. Moreover, reading these references, those of ordinary skill in the art would not have been able to predict that the claimed method would work better than other methods, e.g., administering DNA in saline or encapsulated in microspheres. Thus, the instant claims would not have been obvious. Applicants respectfully request that this rejection be reconsidered and withdrawn.

35 U.S.C. § 102

The Office rejected claims 1, 7, 11, and 14 as allegedly being anticipated by Tite et al. (Immunology. 1990; 70:540-546). Since applicants have canceled claims 1, 7, 11 and 14, this rejection is now moot.

Nonstatutory Obviousness-type Double Patenting

The Office provisionally rejected claims 1-3, 7, 11 -14, 20-22, 32-35, 38, 42-43 and 57-60 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10-13 and 22-28 of copending Application No. 11/178,588 (US200610014714). As it would be more efficient to address this provisional rejection once the

scope of allowable subject matter is determined, applicants defer addressing this rejection until the present claims are found otherwise to be in condition for allowance.

The Office also rejected claim 1 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 7,566,454. Claim 1 has been canceled, thereby rendering this rejection moot.

CONCLUSION

Applicants respectfully request that all claims be allowed. Applicants do not concede any positions of the Examiner that are not expressed above, nor do applicants concede that there are not other good reasons for patentability of the presented claims or other claims. The extension fee in the amount of $555.00 is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 07917-0217002.

Respectfully submitted,

Date: July 6, 2010

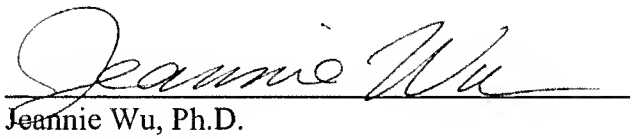

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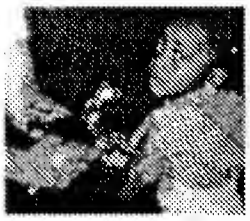
Exhibit A

Jet injector

From Wikipedia, the free encyclopedia

A **jet injector** is a type of medical injecting syringe that uses a high-pressure narrow jet of the injection liquid instead of a hypodermic needle to penetrate the epidermis, the purpose being to reduce the pain associated with needle injection. It is powered by compressed air or gas, either by a pressure hose from a large cylinder, or from a built-in gas cartridge or small cylinder. Some are multi-shot, and some are one-shot. They are made in various shapes, as the links to images below show.



A health worker using a jet injector on a child

They are used by diabetics to inject insulin as an alternative to needle syringes, though they are still not very common.

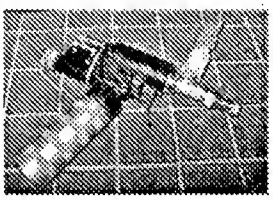
In the *Star Trek* franchise, and sometimes in other fictional scenarios and occasionally in the real world, it is called a hypospray.

Contents

Types of jet injector

Jet Injectors

The **Jet Injector Gun** and the **Ped-O-Jet** are air-powered medical injector devices designed to administer vaccinations in an extremely efficient manner. Invented by Aaron Ismach, these medical devices were bought in mass quantities by the US Government and provided to governments around the world to eradicate smallpox and other diseases. Servicemen in the Armed Forces were routinely injected with these medical devices to immunize them, and civilian usage included vaccinations during flu epidemics and the like. The Jet Injector is powered by electricity, while the Ped-O-Jet version is powered by a foot pump and does not require electricity to administer the vaccines. These devices have various specialized nozzles for different medication densities and also permitted the efficient inoculation of animal populations as well.



A Med-E-Jet vaccination gun from 1980

The **Biojector 2000** is á make of gas-cartridge-powered jet injector. It is claimed that it can deliver intramuscular injections and subcutaneous injections up to 1 milliliter. The part which touches the patient's skin is single-use and can be replaced easily. It can be powered from a big compressed gas cylinder instead of gas cartridges. It is made by Bioject (http://www.bioject.com/biojector2000.html) .

In October 2006 it was in clinical trials for patients using Fuzeon as part of their HAART treatment for HIV. For clinical trial and related information see http://www.hivdent.org/drugs1/drugBIFI0306.htm

History

See also Hypospray#Real-world timeline.

- 19th century: Workmen in France had accidental jet injections with high-powered grease guns [1] (http://www.healthfreelancing.com/samples/nopainIV.php)
- 1920s: Diesel engines begin to be made in large quantities: thus beginning of serious risk of accidental jet-injection by their fuel injectors as workshop accidents.
- 1937: First *known recorded* accidental jet injection by a diesel engine's fuel injector[1].
- 1960: Aaron Ismach invented and patented the Jet Injector medical device which was used for quick mass vaccination for smallpox and other diseases. Ismach was assisted by Dr. Abram Benenson in developing the Jet Injector Gun. The new method met with tremendous success as teams vaccinated large numbers of people at collecting points in the affected countries. The foot operated gun was called the Ped-O-Jet and the electric operated gun was called the Jet Injector Gun.
- 1962: Robert Andrew Hingson claimed to have invented a prototype jet injector and called it the **peace gun**, for quick mass vaccination. But sometimes the injection process dislodged infected matter from a patient onto the nozzle of the injector, risking cross-infection.
- 1964: Aaron Ismach was presented with a Gold Medal from the US Government for his efforts related to the Jet Injector Gun. The Jet Injector also appeared on postage stamps as a commemorative of his efforts.
- September 1966: The Star Trek series started, exposing the public to the idea of jet injectors under the name "hypospray".

- 1976: The USA Agency for International Development published a book called War on Hunger which detailed the War Against Smallpox which Ismach's Jet Injector gun was used to eradicate the disease in Africa and Asia. The US Government spent $150 million a year to prevent its recurrence in North America.
- 1997: The USA Department of Defense, the jet injector's biggest user, announced that it would stop using it for mass vaccinations due to concerns about infection. The DoD order (http://usamma.detrick.army.mil/ftp/mmqc_messages/Q971169.txt) Veterans info page (http://www.hcvets.com/data/transmission_methods/jet_injection.htm)

Accidental jet injection

Accidents have happened in vehicle repair garages and elsewhere where one of these has unintentionally acted as a hypodermic jet injector:

- A fuel injector of a diesel engine.
- A high-pressure grease gun.
- A pinhole leak in a tube supplying a high-powered grease gun from a separate grease pressure-tank.
- A pinhole leak in a tube of high pressure hydraulic oil equipment.
- A high pressure paint spray.
- A pressure washer.

High pressure injections of oil or paint can cause very serious injuries which may require amputation and can induce fatal blood poisoning. Particular care must be taken around high pressure sprays of this kind to avoid such injuries.

References

1. ^ Rees CE. "*Penetration of tissue by fuel oil under high pressure from diesel engine.*" JAMA 1937;109:866-7

External links

- Problems in use of jet injectors by diabetics (http://www.mendosa.com/injector.htm)
- Memory Alpha (Star Trek Wiki) page about the hypospray (http://memory-alpha.org/en/wiki/Hypospray)

Web pages using "hypospray" for a real jet injector

These three references are all to articles in scientific periodicals:-

- Comparison of two steroid preparations used to treat tennis elbow, using the hypospray (http://rheumatology.oxfordjournals.org/cgi/reprint/14/1/47.pdf) (1975)
- The use of the hypospray in the treatment of minor orthopaedic conditions (http://www.jrsm.org/cgi/content/citation/62/6/577) (1969)
- Use of the hypospray jet injector for intra-articular injection (http://ard.bmj.com/cgi/content/citation/26/2/143) (1967)

This link (http://websites.labx.com/rankin/detail.cfm?p=2&autonumber=771) uses the name "hypospray" for an automatic tourniquet.

External links about accidental jet injection

- http://bmj.bmjjournals.com/cgi/content/full/312/7044/1436 (registration required)
- http://www.napavalleypetroleum.com/msds_napa_no2_diesel_fuel.htm (scroll down to section 7)

Retrieved from "http://en.wikipedia.org/wiki/Jet_injector"
Categories: Medical equipment | Drug delivery devices | Dosage forms